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Mini-Review

Role of the macrophage and its polarization in liver inflammatory disorders

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ABSTRACT

Macrophages play an important role in the process of liver infection, inflammation and disease. Liver macrophages mainly include Kupffer cells and infiltrating monocyte-derived macrophages. After being stimulated, liver macrophages can be polarized into pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages. M1 macrophages mainly secrete pro-inflammatory cytokines and exert host immune function; M2 macrophages secrete anti-inflammatory cytokines, which are involved in repair and regeneration after injury. In this review, we focus on the potential roles of macrophages in inflammatory liver disorders, especially emphasizing the polarization of macrophages during liver inflammation, and their effects on the progress and outcomes of liver diseases.

KEYWORDS: macrophage, polarization, liver, inflammation.

1. Introduction

Liver has a unique innate immune environment, which is an essential defense system of the body, playing an important role in the inflammatory response [1]. Macrophages are one of the major immune cells in the liver, which perform crucial function in maintaining liver homeostasis and modulating disease status [2]. Macrophages are particularly abundant in the liver compared to other organs and tissues. It has been showed that 20 to 40 macrophages are present in every 100 hepatocytes [3]. Liver macrophages mainly include Kupffer cells and infiltrating monocyte-derived macrophages [4]. One of the major functions of macrophages is phagocytizing pathogens and dead cells during inflammation; they are also involved in antigen presentation and secrete various cytokines through antigen processing of major histocompatibility complex (MHC) molecules [5]. Kupffer cells account for 20 to 35% of all non-parenchymal cells in the liver, which play an important role in the liver homeostasis and the initiation, progression and convergence of liver inflammation [6]. In addition, they act as an antigen presenting cell (APC), providing a bridge between the innate immune system and the adaptive immune system [7]. The occurrence of liver injury causes activation of the Kupffer cells, which release inflammatory cytokines and chemokines, promoting the infiltration of monocytes into the liver, and producing a large number of inflammatory monocyte-derived macrophages [8]. It may thus become a new strategy for controlling liver diseases by modulating macrophages. Therefore, it is necessary to fully understand the behaviors of macrophages in the liver during

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different circumstances [1]. Here in this review, we will summarize the concept, origin, polarization, and phenotype of macrophages, and discuss the role of macrophages in liver inflammatory diseases.

2. Liver macrophage: the concept and origin

According to the traditional concept in immunology, macrophages are derived from monocytes. The circulating monocytes are recruited to the site of inflammation and differentiate into macrophages in tissues during inflammation [9]. Macrophages are found in almost all tissues. Macrophages in the liver are mainly Kupffer cells and monocyte-derived macrophages (Mo-Mfs), which originate from yolk sac-derived specific progenitor cells and are inoculated during embryogenesis [4]. Kupffer cells are highly efficient phagocytic cells that recognize, ingest, and degrade cell debris, foreign bodies, or pathogens [10]. In homeostasis, the balance of Kupffer cells in the body supports a tolerant immune response, while they also have scavenger, complement, and pattern recognition receptors that are activated in response to infectious or noninfectious threats to induce an immunogenic T cell response [8]. However, macrophages derived from infiltrating monocytes mainly have two kinds of circulating monocytes: high-6C(Ly-6Chigh) and low-6C(Ly-6Clow), which express monocytes [11]. High Ly-6C can express chemokine receptors, pattern recognition receptors and cytokines [12], while low Ly-6C exhibits patrol behavior and expresses more scavenging receptor behavior [13]. In the event of liver injury, Kupffer cells combine with other liver cells to secrete chemokines (such as CCL2), triggering a rapid, transient mechanism to expand the macrophage pool through inflammatory phagocytes and recruitment of new Mo-Mfs [8].

3. Macrophage polarization: M1 and M2 macrophages

Macrophage polarization refers to activation of macrophages towards different directions, upon various stimuli and circumstances. Polarization status is not fixed; macrophages could respond to it, and integrate multiple signals from microbes, damaged tissues and normal tissue environments [14]. However, currently two major polarization status of macrophages are identified, namely M1 macrophages with pro-inflammatory effects and M2 macrophages with anti-inflammatory effects, which show somehow opposite effects during pathogenesis or tissue damage [15].

Regarding the activation/polarization of macrophages, at least four definitions have been pointed out [16]. The first concept of M1/M2 macrophage come from the different immune response and behaviors of macrophages in which M1 macrophages are formed during intracellular infection mediated by interferon-γ (IFN-γ) derived from Th1 cells, while M2 macrophages are activated during extracellular parasitic infection with the production of interleukin-4 (IL-4), in which IL-4, IFN-γ and lipopolysaccharide (LPS) exhibit different effects on macrophage gene expression [17]. Mills and his colleagues raised another notion, in which macrophages could behave differently as M1 and M2 phenotypes, the concept being that macrophages derived from the prototype Th1 strain (C57BL/6, B10D2) are more easily activated by IFN-γ or LPS to produce nitric oxide (NO), than the macrophages derived from the Th2 strain. In contrast, when macrophages derived from Th2 cells were stimulated by LPS, the arginine metabolism was converted to ornithine metabolism in macrophages. The M1 and M2 macrophages showed not only different metabolisms, but behaved oppositely during inflammatory process [18]. Further, Murray and other researchers extended the M1 and M2 definition to different subclasses by considering the different activation procedures, such as M2a, M2b and so on [16]. In addition, recently Joshi and his colleagues indicated that macrophages stimulated by granulocyte-macrophage colony stimulating factor-1 (GM-CSF-1) and macrophage colony stimulating factor-1 (CSF-1) are responsive to M1 and M2 macrophages, respectively [19].

Accordingly, recently Mantovani and his colleagues proposed a model of M1-M2 macrophage, in which M1 macrophages are generally recognized and activated by IFN-γ + LPS or tumor necrosis factor (TNF), to secrete pro-inflammatory cytokines such as TNF-α, IL-1α, IL-1β, IL-6, IL-12, cox-2 and IL-10; for M2 macrophages, M2a is induced by IL-4 and IL-13 which secretes IL-10, TGF-β, CCL17 and so on. M2b is induced by immune complexes and toll-like receptors (TLR) or IL-1R

agonists, which secrete TNF-α, IL-1β, IL-6, IL-10 and CCL1; M2c is induced by IL-10, TGF-β and glucocorticoids which secrete IL-10, transforming growth factor-β (TGF-β), C-C motif chemokine ligand 16 (CCL16), CCL18 and C-X-C motif chemokine ligand 13 (CXCL13). In addition, it has also been reported that M2d, the fourth category of M2 macrophages, is induced by TLR agonists through adenosine receptor ligands and it secretes IL-10 and vascular endothelial growth factor (VEGF) [5, 20]. There are some differences in the cytokine generation accounting for M1 and M2 macrophages. For example, both M1 and M2 secrete IL-10 and IL-12, but M1 macrophages usually secrete high levels of IL-12 and low levels of IL-10. M2 macrophages, on the other hand, secrete low levels of IL-12 and high levels of IL-10 [20]. Table 1 summarizes the polarization and functions of M1/M2 macrophages.

4. Role of macrophages in inflammatory liver diseases

Macrophages play an important role in the immune homeostasis of the liver. The phagocytosis of macrophages is not only used for nutrient acquirement, clearance of degenerated and apoptotic cells, but also functioned as a host defense mechanism against invading pathogens [21]. Immune homeostasis of the liver is largely regulated by the mononuclear phagocyte system, including Kupffer cells and Mo-Mfs, which forms a dynamic, complicated, and highly active network that constitutes the primary defense against microbial invasion [1]. Meanwhile, the mononuclear phagocyte system maintains tissue homeostasis by secreting cytokines such as IL-10 to promote liver immune tolerance [22].

4.1. Acute liver injury

Acetaminophen (APAP)-induced acute liver injury is a representative acute liver injury, and it is becoming a worldwide problem with a mortality rate of 5% in the population not receiving treatment. However, the population mortality rate will be reduced to 1% if acetylcysteine is given within 8 hours of poisoning [23]. In the body, APAP is converted to N-acetyl-p-benzoquinone imine (NAPQI), a radical, by cytochrome CYP2E1 which will be detoxified by glutathione (GSH). However, excess and continuous generation of NAPQI will deplete GSH, consequently leading to mitochondrial oxidative stress, DNA damage, mitochondria dysfunction and so on [24, 25], finally resulting in necrosis of liver [26]. It has been reported that in APAP-induced acute liver injury, Kupffer cells are first activated, followed by increase in M1 macrophages which were mostly derived from recruited mononuclear cells; all of these promoted the inflammatory process of liver injury [27]. However, with the progression of the disease, the expression of M2 macrophages was increased, while the expression of M1 macrophages decreased gradually, whereby M2 macrophages become predominant macrophages to serve for liver repair [27]. In our recent study, we also found the significantly increased marker molecules of M2 macrophages, i.e., IL-10, TGF-beta and Arg-1at 48 h after APAP administration which is the repair stage of APAP-induced liver injury (Figure 1).

Table 1. Polarization and function of M1/M2 macrophages.

Phenotype		Inducible factor	Marker	Function
M1		IFN-γ, LPS, TNF	TNF-α, IL-1α, IL-1β, IL-6, IL-12, cox-2 and IL-10 etc.	Pro-inflammatory effect
M2	M2a	IL-4, IL-13	IL-10, TGF-β, CCL17 etc.	Anti-inflammatory effect
	M2b	Immune complexes, TLR or IL-1R agonists	TNF-α, IL-1β, IL-6, IL-10 and CCL1 etc.	
	M2c	IL-10, TGF-β and glucocorticoids	IL-10, TGF-β, CCL16, CCL18 and CXCL13 etc.	
	M2d	TLR agonists	IL-10, VEGF	

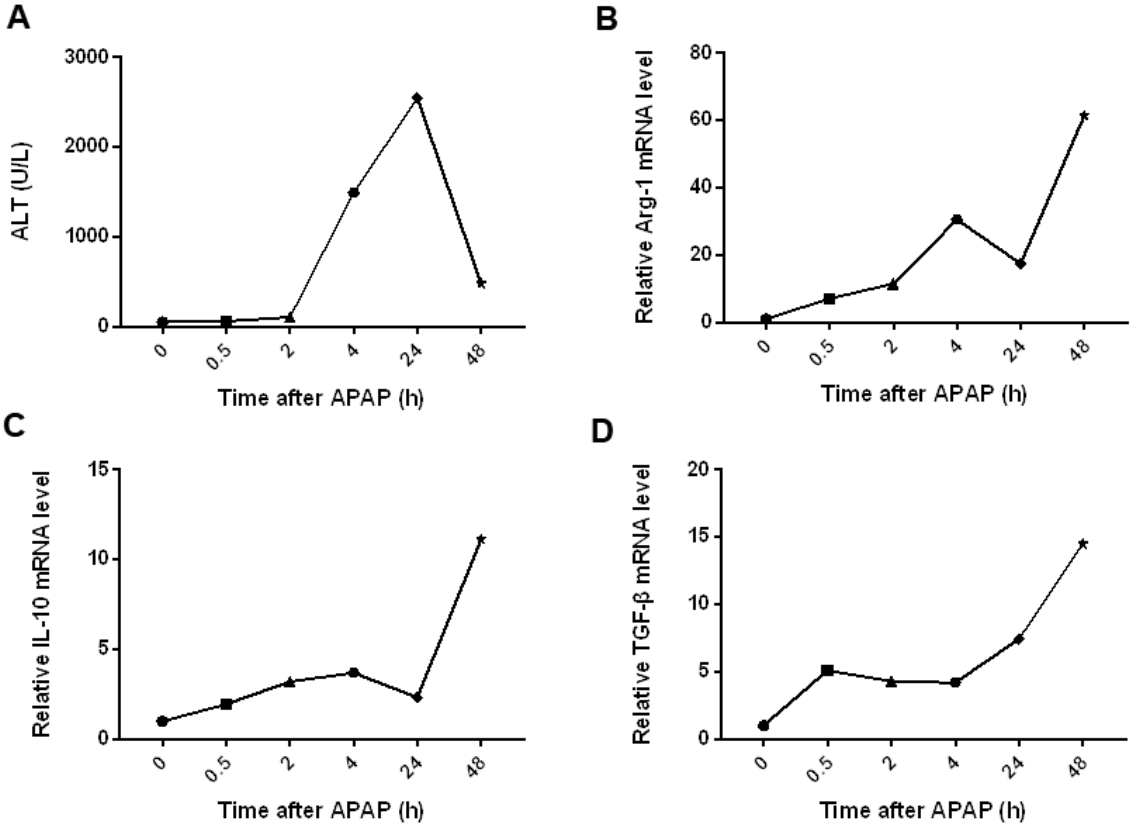

Figure 1. Expression of macrophages and serum ALT at different time points of APAP-induced acute liver injury in mice.

These findings strongly suggested that during the process of liver injury and repair, M1 macrophages and M2 macrophages could transform dynamically to maintain the body's homeostasis [5].

4.2. Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is due to the deposition of fat in hepatocytes but without other symptoms associated with steatosis [28]. Regarding the role of macrophages in NAFLD, it has been shown that TNF-producing Kupffer cells play a crucial role in the early stages of steatotic hepatitis by triggering inflammation and promoting monocyte recruitment [29]. Another study using mice with clodronate and high-fat diets showed that hepatic steatosis was reduced when Kupffer cells were depleted, and Kupffer cells could promote steatosis by IL-1β-dependent inhibition of peroxisome proliferator-activated receptor-α (PPAR-α) [30]. In addition to Kupffer cells, monocyte-derived macrophages recruited in liver also play an important role in the pathogenesis of NAFLD. When liver inflammation occurs, CCR2 is highly expressed in monocyte-derived macrophages, resulting in the recruitment of circulating macrophages to the liver, which then rapidly differentiate into pro-inflammatory macrophages [31]. Accumulation of liver macrophages is considered to be a hallmark of progressive liver disease in patients with alcoholic liver disease [32]. In patients with alcoholic liver disease, macrophages are particularly abundant in the portal vein. The increase in macrophage-related biomarkers (e.g., TNF, CCL2, reactive oxygen species (ROS) in circulation indicates that liver macrophages play a key role in promoting inflammation in alcoholic liver injury [33]. In severe alcoholic hepatitis, high expression of hepatic portal endotoxin and increased intestinal permeability strongly stimulate Kupffer cells, which may be responsible for the above results [34].

4.3. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is most frequently found in patients with liver disease characterized by chronic inflammation [35]. Liver macrophages play an important role in the development of hepatocellular carcinoma; they provide a pro-inflammatory carcinogenic environment and are involved in anti-tumor immune response [1]. Tumor-associated macrophages (TAMs) act as immunosuppressive cells to stimulate tumor growth. It has been known that TAMs promote tumorigenesis through different ways: (1) they could release many angiogenic factors, such as VEGF, platelet-derived growth factor (PDGF), TGF-β and so on, to stimulate tumor angiogenesis; (2) They could also secrete signal factors, growth factors and matrix metalloproteinase to activate tumor-epithelial-mesenchymal transformation, promoting invasion and metastasis of tumor; (3) TAM could promote the formation of cancer stem cells through generation of related cytokines and molecules; (4) TAMs increase T-reg cells and myeloid-derived suppressor cells by negative regulation of cytotoxic effector cells and through the interaction of cytokines and related enzymes with surface receptors [36]. All the above functions of TAMs provide a good microenvironment for tumor formation and development. A recent study indicated that TAM could be derived from abundant extracellular vesicles, showing unique proteomic features that enhance thrombus formation in cancer cells and promote T cell activation and proliferation [37]. On the contrary, although the above functions of liver macrophages are conducive to the occurrence and development of tumors, they also play a crucial role in the anti-tumor process. Eggert reported that hepatocytes secrete CCL2 after senescence, which recruits CCR2+ pro-inflammatory monocyte-derived macrophages to eliminate precancerous senescent cells, consequently preventing the formation of HCC [38].

4.4. HBV

Hepatitis B virus (HBV) infection remains a major global health problem with more than 250 million patients in the world [39]. A much larger number of Kupffer cells were observed in the liver of HBV patients than healthy people [40]. Moreover, pro-inflammatory mononuclear cells are rapidly recruited to the liver after viral infection, and the number eventually exceeds the number of resident Kupffer cells [41]. In the liver, Kupffer cells and monocyte-derived macrophages can be infected with HBV virus, causing the expression of pro-inflammatory cytokines and activating NK cells, which is beneficial for HBV infection [42]. In addition, Kupffer cells produce immune regulatory mediators such as IL-10, TGF-β, galactose-9, programmed death ligand 1 (pd-l1) and programmed death ligand 2 (pd-l2) during chronic HBV infection to inhibit antiviral T cell responses [43]. During HBV infection, HBV can also stimulate the function of Kupffer cells. For example, HBV particles and HBsAg can induce the generation of IL-1β, IL-6, CXCL8 and TNF from CD68+ non-parenchymal cells through activation of NF-κB, consequently inhibiting HBV replication in hepatocytes [44]. In contrast, it was also reported that HBV could also inhibit the function of Kupffer cells. HBV could actively interfere with the pro-inflammatory function of Kupffer cells, by means of impeding TLR pathway, RIG-I signal transduction and pro-inflammatory activity of hepatocytes, to avoid host immunity [45].

5. Macrophage reprogramming for treatment of diseases

As described above, macrophages play important roles in the initiation and progression of many diseases. Hence it is reasonable to develop therapeutic strategy by modulating macrophage polarization, namely macrophage reprogramming. For example, in the case of tumors, the increase in TAMs is associated with poor prognosis of cancer patients [46]. TAMs exhibit multiple phenotypes with multiple functions depending on the tumor microenvironments [47]. Among them, M1-type macrophages with anti-tumor properties and M2-type macrophages with tumor promotion functions were the major phenotypes of TAM. M1-type macrophages could usually be selected from TAMs or reprogrammed from M2-type macrophages by TLR agonists, monoclonal antibodies targeting M1 phenotypes, and other compounds [48]. Thus, TLR agonists may become a promising antitumor therapy, which was reported to induce nuclear translocation of NF-κB in J774A macrophages

followed by production of pro-inflammatory proteins such as TNF-α, IL-6, IL-12, and CCL2 [49]. Another strategy is to stimulate CD40 that shows anti-tumor T cell response, by using monoclonal antibodies [50]. Macrophages express CD40 in the plasma membrane, and anti-CD40 monoclonal antibodies can promote the tumor-killing activity of macrophage by enhancing the generation of NO and TNF-α [48]. Use of chemicals such as INF-γ, is also a useful method to trigger the reprogramming of TAM [51]. Reprogrammed macrophages could release cytokines and chemokines including INF-γ to activate CD8+ T cell [52].

6. Conclusions

Macrophages play a critical role in liver injury and inflammation, and their origin and polarized phenotypes are different in different liver disease status. It is known that liver macrophages mainly include Kupffer cells and infiltrating monocyte-derived macrophages, which can be polarized into M1-type macrophages secreting proinflammatory cells and M2-type macrophages secreting anti-inflammatory cells. A clear understanding of the function of different macrophage phenotypes can further elucidate the polarization status of macrophages in different liver diseases and their effects on the progression and outcome of diseases. Due to the central role of macrophages in the liver, they offer many promising options for the treatment of liver diseases. In addition, deepening the understanding of macrophage reprogramming can provide new ideas and methods for the development of treatment methods for some diseases such as cancer. Future studies are warranted for the development of new therapeutic strategies by modulating macrophages.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest associated with this manuscript.

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